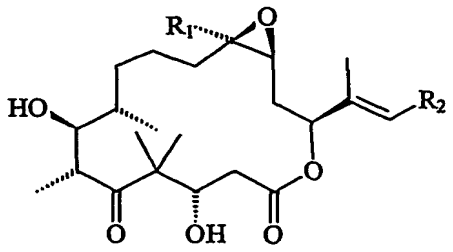
What we claim is:

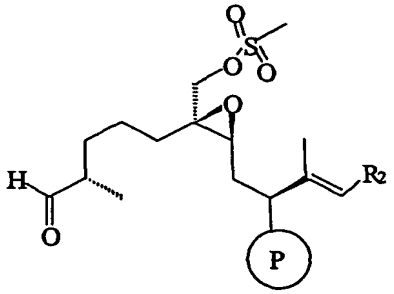
1. Process for the preparation of epothilone derivatives of formula 9



(9)

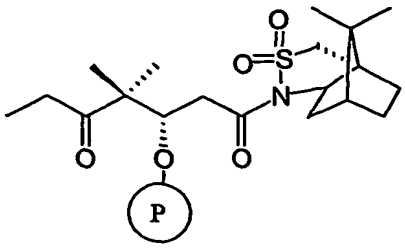
wherein
R1 is methyl and R2 has the meaning of an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl or an unsubstituted or substituted heterocyclic radical fused to a benzene nucleus and salts thereof with metal cations, characterised by

a) reacting a compound of formula 1



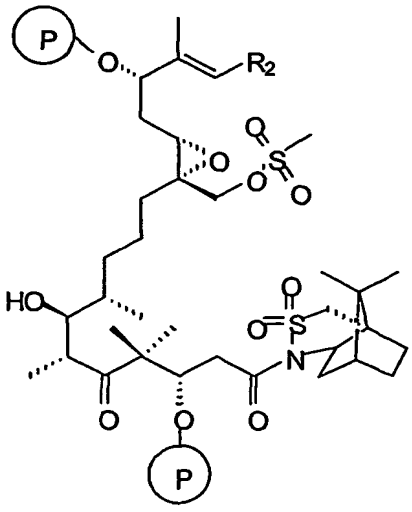
(1)

wherein R2 has the meanings given above and the mesylate group may be replaced by a tosylate group and the and the mesylate group may be replaced by a tosylate group and the like and (P) is an alcohol protecting group ,with a sultam derived compound of formula 2 *as, for example,*



(2)

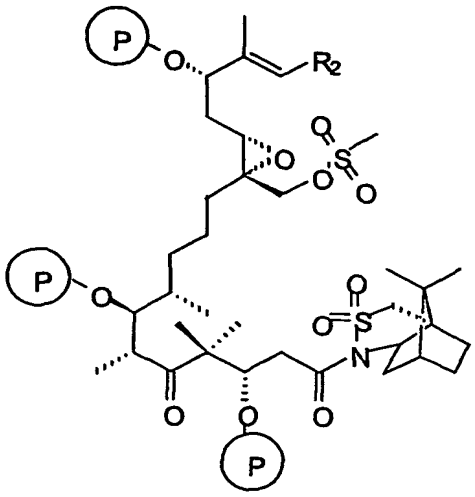
in a selective aldol reaction in the presence of a Lewis acid and addition of a base in an inert solvent at lower tempeartures between -50° to -100°C and thereafter at elevated temperatures between -20° to +20°C obtaining a compound of formula 3



(3)

wherein R2 and P have the above given meanings, and

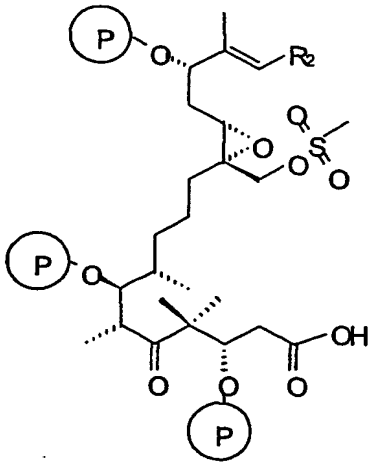
b) the obtained compounds of above formula 3 are reacted at temperatures between –70° and 25° C in the presence of a silyl-ether forming compound and 2,6-lutidine forming compounds of formula 4



(4)

wherein R2 and  have the meanings given above, and

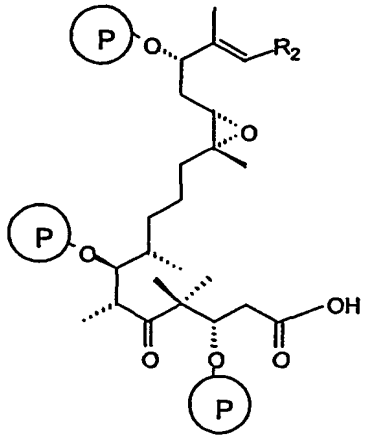
c) converting an above compound of formula 4 to the carboxylic acid by splitting off the chiral auxillary group with TBAOH/H2O2 in DME or LiO2H in THF/MeOH/H2O obtaining a compound of formula 5



(5)

wherein R2 and  have the meanings given above, and

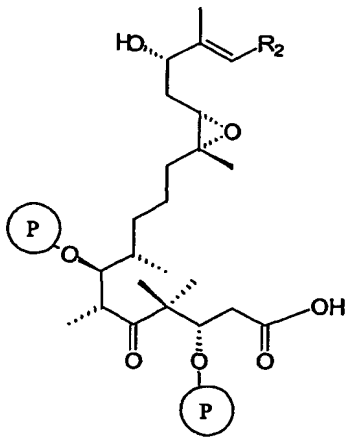
d) reacting compounds of above formula 5 with a reducing reagent in an inert solvent cleaving the mesylate or tosylate group or the like obtaining a compound of formula 6



(6)

wherein R2 has the above given meanings.

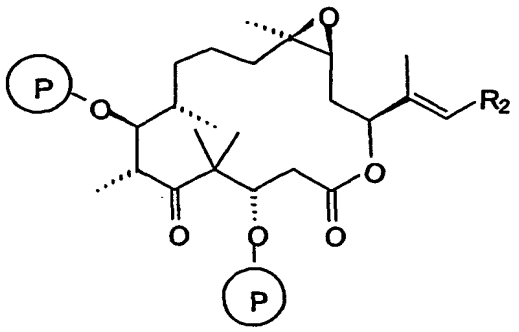
e) hydrolysing the compounds of above formula 6 with a desilylation reagent or an acid in an inert solvent or a mixture thereof, e.g. TASF or HF·pyridine in THF, obtaining a selectively desilylated compound of formula 7



(7)

wherein R2 and  have the above given meanings, and

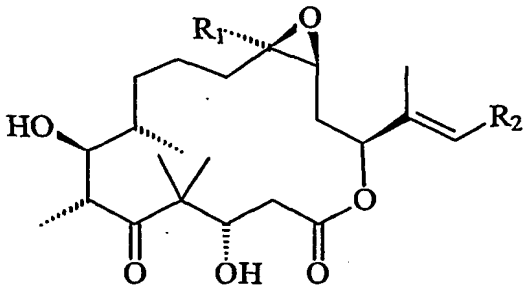
f) macrolactonizing obtained compounds of formula 7 according to the conditions described by M. Yamaguchi et al Bull.Chem.Soc.Jpn.,1979, 52 ,1989, obtaining a fully protected epothilone derivative of formula 8



(8)

wherein R2 and  have has the above defined meanings, and

g) treating an obtained compound of formula 8 with HF·pyridine in an inert solvent at temperatures between 0° and 30 °C and cleaving both silyl protecting groups obtaining epothilone derivatives of formula 9



(9)

wherein R1 is methyl and R2 has the above described meanings and optionally converting compounds of formula 9 wherein R1 and R2 have the defined meanings under formula 9 to a salt with metal cations by conventional methods.

2. Process according to step a) of claim 1, characterised, that compounds of formula 1 are reacted with a compound of formula 2, for example, in the presence of TiCl4 and Hünig base

(iPr2Net) in dichloromethane at a temperature of –78 °C and thereafter at a temperature of 0 °C obtaining new compounds of formula 3.

3. Process according to step b) of claim 1, characterised that obtained compounds of formula 3 are reacted with a silyl-ether forming compound in the presence of 2,6-lutidine at temperatures between –20° and +20 °C, especially at a temperature of –10 °C in dichloromethane as inert solvent forming compounds of formula 4.

4. Process according to step c) of claim 1, characterised that obtained compounds of formula 4 are converted to the carboxylic acid by splitting off the chiral auxillary group with TBAOH/H2O2 in DME or LiO2H in THF/MeOH/H2O obtaining a compound of formula 5.

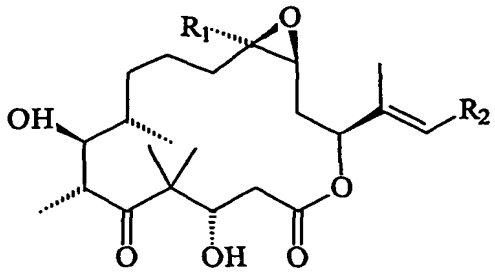
5. Process according to step d) of claim 1, characterised that obtained compounds of formula 5 are reacted with LiBHEt3 as reducing reagent in THF as inert solvent for cleaving the mesylate or tosylate group or the like obtaining a compound of formula 6.

6. Process according to step e) of claim 1, characterized that obtained compounds of formula 6 are hydrolysed with a desilytation reagent especially with TASF or an organic acid especially HF·pyridine in an inert solvent, e.g. pyridine or THF, obtaining compounds of formula 7.

7. Process according to step f) of claim 1, characterised that obtained compounds of formula 7 are macrolactonized according to Yamaguchi et al, e.g. treating the hydroxy-acid with Et3N and 2,4,6-trichlorobenzoyl chloride at lower temperature, e.g. 0 °C and thereafter the reaction mixture is added to a solution of 4-DMAP in toluene and the temperature raised to ca. 75 °C obtaining compounds of formula 8.

8. Process according to step g) of claim 1, characterized that obtained protected epothilone derivatives of formula 8 are treated with HF·pyridine in pyridine as inert solvent and after cleavage of both protecting groups (P) epothilone derivatives of formula 9 are obtained and optionally converting compounds of formula 9 wherein R1 and R2 have the defined meanings under formula 9 to a salt with metal cations by conventional methods.

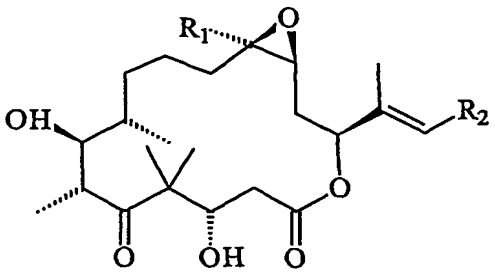
9. Compounds of formula 9



(9)

wherein R1 is methyl and R2 is an unsubstituted or substituted aryl and salts with metal cations.

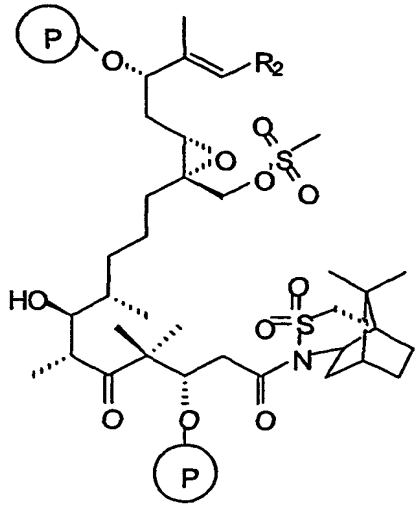
10. Compounds of formula 9



(9)

wherein R1 is methyl and R2 is an unsubstituted or substituted phenyl and salts with metal cations.

11. Compounds of formula 3

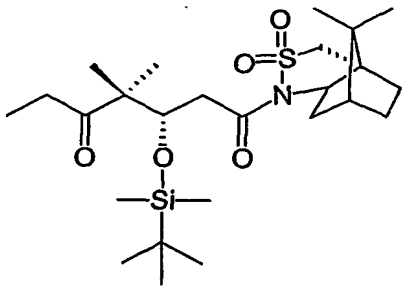


(3)

wherein R2 has the meanings given under formula 9.

12. Process for the production of compounds of formula 3, characterised that a compound a compound of formula 1

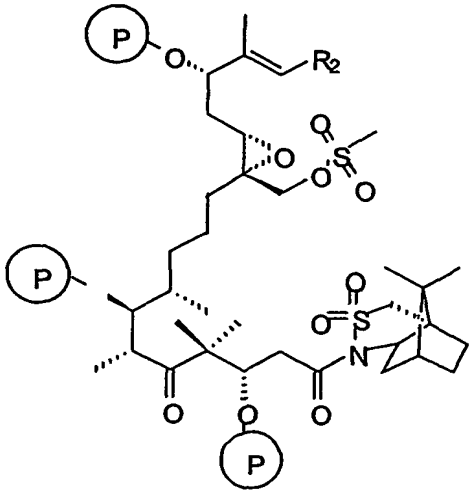
wherein R2 has the above given meanings and the mesylate group may be replaced by a tosylate group and the like in all following reaction sequences with a sultam derived compound of formula 2 as for example



(2)

in a selective aldol reaction in the presence of a Lewis acid and addition of a base in an inert solvent at lower temperatures between –50° to –100 °C and thereafter at elevated temperatures between –20° to +20 °C obtaining a compound of formula 3.

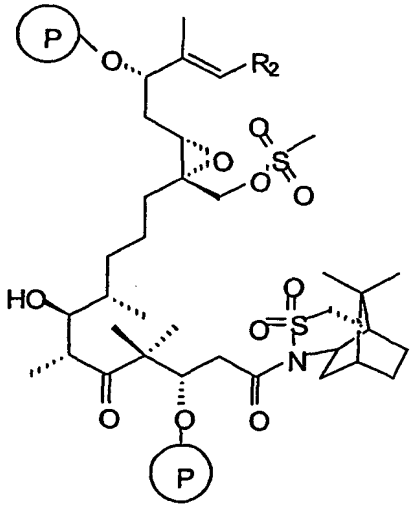
13. Compounds of formula 4



(4)

wherein R2 has the above meanings.

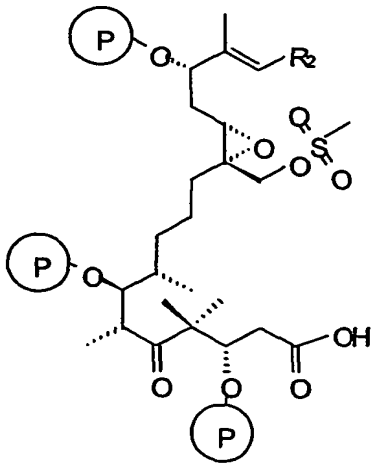
14. Process for the production of new compounds of formula 4, characterised that compounds of formula 3



(3)

are reacted at temperatures between –70° and 25 °C in the presence of an silyl-ether forming compound and in the presence of 2,6-lutidine forming compounds of above given formula 4.

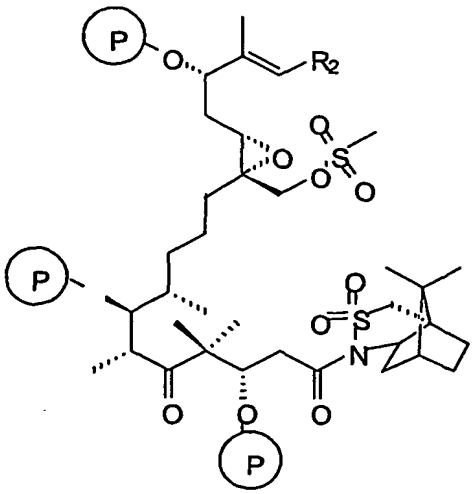
15. Compounds of formula 5



(5)

wherein R2 has the meanings given above.

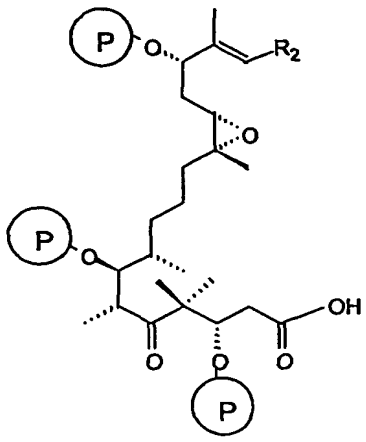
16. Process for the production of new compounds of formula 5 characterised that compounds of formula 4



(4)

are converted to carboxylic acids by splitting off the chiral auxillary group with TBAOH/H2O2 in DME or LiO2H in THFMeOH//H2O obtaining a compound of formula 5.

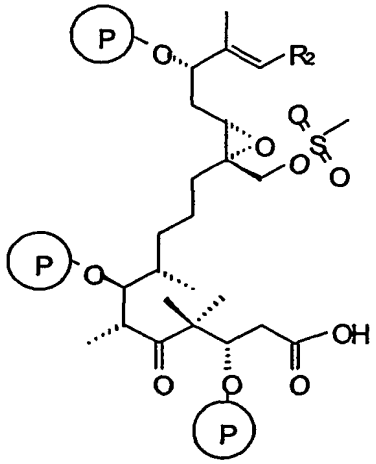
17. Compounds of formula 6



(6)

wherein R2 has the above given meanings.)

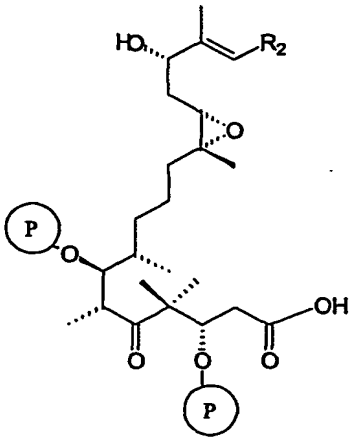
18. Process for the production of new compounds of formula 6, characterised in that compounds of formula 5



(5)

are reacted with a reducing reagent in an inert solvent cleaving the mesylate group or tosylate group or the like obtaining a compound of above formula 6.

19. Compounds of formula 7

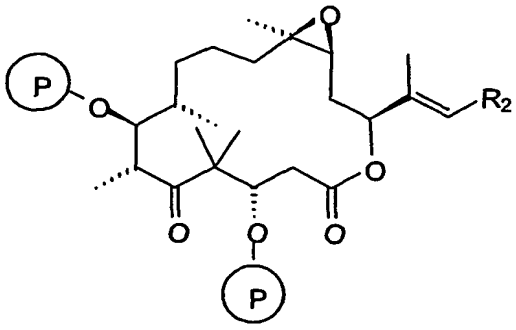


(7)

wherein R2 has the above given meanings.

20. Process for the preparation of new compounds of formula 7, charaterised by hydrolysing the tri-protected tris-silylether compounds of above formula 6 with a desilylation reagent, especially TASF or an organic acid, especially HF·pyridine in an inert solvent, e.g. pyridine or THF, obtaining a compound of formula 7.

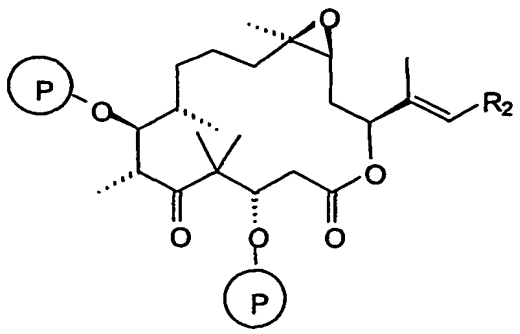
21. Compounds of formula 8



(8)

wherein R2 has the above given meanings.

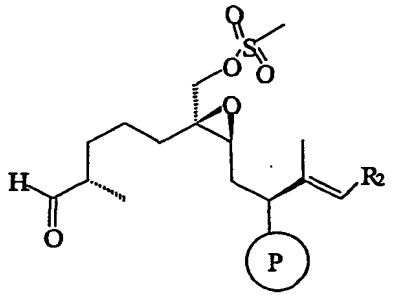
22. Process for the production of compounds of formula 8, characterised by macrolactonizing compounds of formula 7 according to the conditions described by M. Yamaguchi et al Bull.Chem.Soc.Jpn.,1979, 52 ,1989, obtaining a fully protected epothilone derivative of formula 8



(8)

Wherein R2 has the above given meanings.

23. Compounds of formula 1

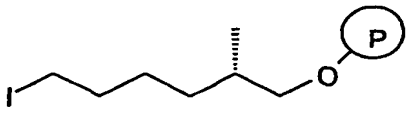


(1)

wherein R2 has the meaning of an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl or an unsubstituted or substituted heterocyclic radical fused to a benzene nucleus.

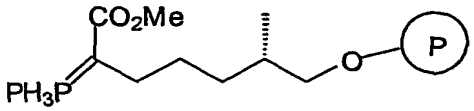
24. Process for the production of compounds of formula 1, characterised by

a) reacting a compound of formula X



(X)

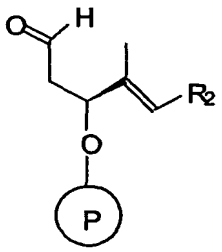
with PPH3 at temperatures between 50 ° - 150 °C, more precisely at a temperature 100° C and thereafter with KHMDS in an inert solvent, especially in THF at 0°C and thereafter cooling the reaction mixture to a temperature between –50 ° to –100 °C, and treating with CH3CO2Cl more precisely at a temperature of –78 °C obtaining a compound of formula XI



(XI)

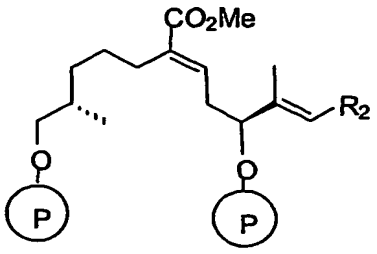
and,

b) reacting the obtained compound of formula XI with a compound of formula XII



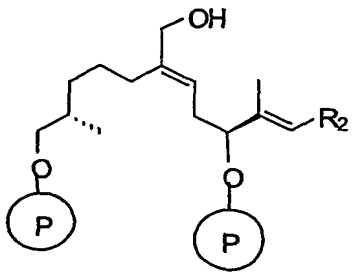
(XII)

in an inert solvent, e.g. in toluene at temperatures between 20° to 60 °C, more precisely at a temperature of 40 °C obtaining a compound of formula XIII



(XIII)

c) reducing a compound of formula (XIII) with a reducing agent, especially with DIBALH, in an inert solvent, e.g. toluene at temperatures between –50° to –100 °C, more precisely at a temperature of –78 °C and thereafter elevating the temperature to 0 °C obtaining a compound of formula XIV

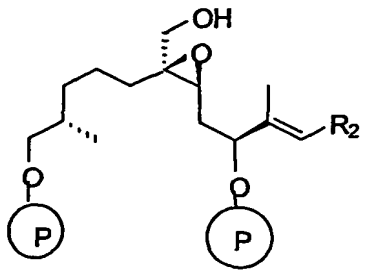


(XIV)

(the drawing of formula XIV and the following compounds thereafter have been simplified),

R2 and  have the above meanings, and

d) using the conditions under Sharpless [(+)-diethyl-L-tartrate, Ti(OPr)4, t-BuOOH] for epoxidation of a compound of formula XIV obtaining a compound of formula XV

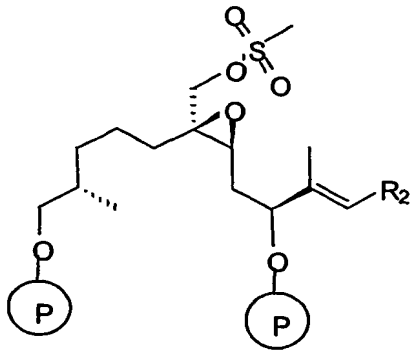


(XV)

wherein R2 and  have the above given meanings under formula 9 and formula 1 respectively.

The obtained compound of formula XV is a new compound and is used as precursor for the next step e) of the process sequence, and

e) introducing the mesylate group into a compound of formula XV by adding mesylate chloride (the mesylate group may be replaced by a corresponding tosylate group or the like) in the presence of triethylamine (Et_3N) in an inert solvent, e.g. dichloromethane obtaining a compound of formula XVI

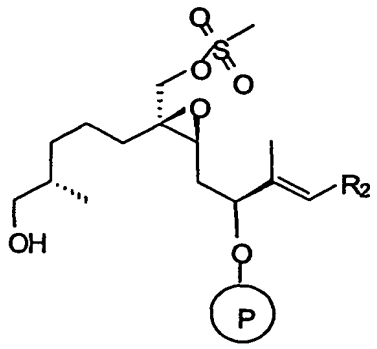


(XVI)

wherein R2 and  have the above given meaning.

The obtained compound of formula XVI is a new compound and is used as intermediate for the next step f), and

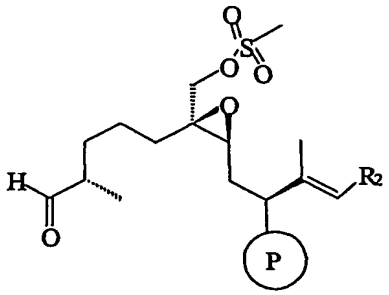
f) treating the obtained compound of formula XVI with an organic acid in an inert solvent, more precisely with pyridinium p-toluenesulfonate or camphor sulfonic acid in absolute ethanol, hydrolysing the one protecting groups and obtaining a compound of formula XVII



(XVII)

wherein R2 has the above given meanings, and

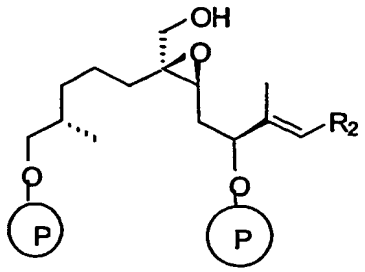
g) oxidizing by using the Swern-oxidation method, e.g. oxidizing the alcoholic group by the promotion of oxalyl chloride and activation of dimethyl sulfoxide, passing the alkoxysulfonium salts and after addition of a base and intramolecularly rearrangement obtaining a keto compound of formula 1



(1)

wherein R2 and  have the above given meanings.

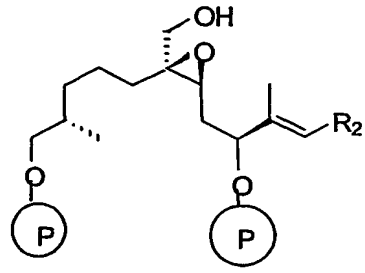
25. Compounds of formula XV



(XV)

wherein R2 and  have the above given meanings.

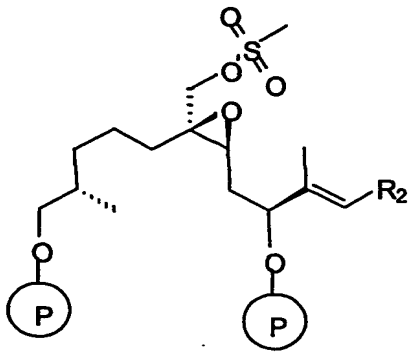
26. Process for the production of compounds of compounds of formula XV, charcterised by using the conditions under Sharpless [(+)-diethyl-L-tartrate, Ti(OPr)4, t-BuOOH] for epoxidation of above compound of formula XIV obtaining a compound of formula XV



(XV)

wherein R2 and  have the above given meanings under formula 9 and 1 respectively

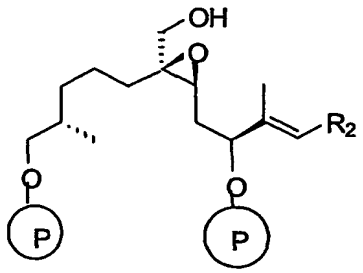
27. Compounds of formula XVI



(XVI)

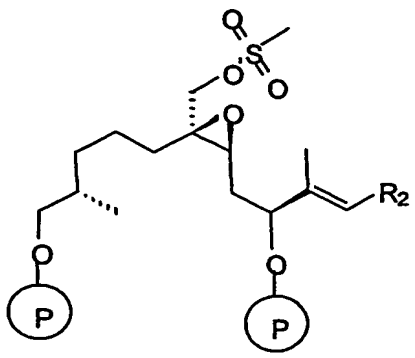
wherein R2 and P have the above given meanings.

28. Process for the production of compounds of formula XVI,
characterised by introducing the mesylate group or tosylate group or the like into a compound of formula XV



(XV)

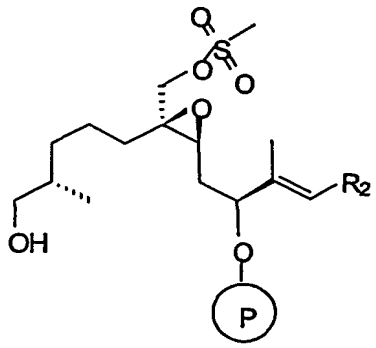
by adding mesylate chloride (the mesylate group may be replaced by a corresponding tosylate group or the like) in the presence of triethylamine (Et_3N) in an inert solvent, e.g. dichloromethane obtaining a compound of formula XVI



(XVI)

wherein R2 and P have the above given meaning.

29. Compounds of formula XVII

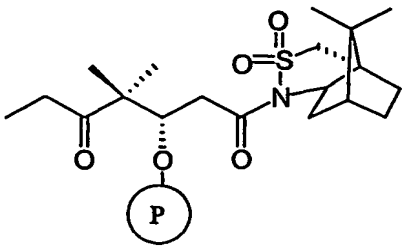


(XVII)

wherein R2 and P have the above given meanings.

30. Process for the production of compounds of formula XVII, charaterised by treating the obtained compound of formula XVI with an organic acid in an inert solvent, more precisely with pyridinium p-toluenesulfonate or camphor sulfonic acid in absolute ethanol, hydrolysing the protecting group P and obtaining a compound of formula XVII.

31. A new compound of formula 2



(2)

32. A method of treatment of a warm-blooded animal suffering from a cancer disease and that is in need of such treatment, comprising administering a compound of the formula 9 wherein R2 is an unsubstituted or substituted aryl radical or a pharmaceutically acceptable salt thereof, according to claim 9 to said warm-blooded animal in an amount that is sufficient for said treatment.

33. A pharmaceutical composition that is suitable for administration to a warm-blooded animal for the treatment of a cancer disease, comprising an amount of an active ingredient of the formula 9 wherein R2 is an unsubstituted or substituted aryl radical according to claim 9, which is effective for the treatment of said cancer disease, together with at least one pharmaceutically acceptable carrier.

34. Use of a compound of formula 8 for preparing a compound of formula 9 for medical treatment.